Summary

(1) Lowering of the basal metabolic rate was effected in nearly all cases, irrespective of the kind of iodine used.

(2) The two methods of treatment produced practically the same diminution in the basal metabolic rate and in about the same length of time.

(3) It was found necessary to give nearly four times as much resublimed iodine as Lugol's solution to produce the same clinical result.

A CLINICAL STUDY OF THE COLLOIDAL BENZOIN REACTION

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THE Wassermann reaction, globulin content, cell count and pressure of the cerebro-spinal fluid as measured by millimeters of mercury, have been the chief diagnostic measures the laboratory has used to aid the clinician in diagnosing neurological lues and separating the same from other neurological lesions. Lange described his colloidal gold test in 1912 and in 1914 Lee and Hinton described a technique for performing the Lange colloidal gold test which was followed by numerous articles on this subject. Nearly every investigator has found difficulty in making a colloidal gold solution that was satisfactory in all respects. The test is used a great deal and is of great help but a simpler test that is reliable would be very welcome. The Emanuel mastic test was described in 1917 but has not found great favour.

In 1921 Guillain, Laroche and Lechelle described a colloidal benzoin test which is very simple and in my hands seems to give reliable data; this test has not come into general use and this study was done to determine its reliability and confirm or nullify the findings of other workers. Of course this cannot take into consideration the essential inequality of the technique of the various workers. At the commencement of this investigation it was thought this test would assist in corroborating the clinical and other serological diagnoses but as the work advanced it seemed that a clinical diagnosis could almost be built up on the result of the test.

The technique is very simple and does not necessitate elaborate laboratory equipment, but chemically clean glassware is essential. Freshly distilled water carefully protected from the atmosphere is the only diluent required. The spinal fluid should be absolutely blood free, that is cell and serum free, as these will give a broader zone and be unreliable. It should be as fresh as possible, though it was found that fluids twenty-four hours old give reliable readings but the zone was a little broader. Experiments were carried out to investigate these factors and will be demonstrated graphically in the accompanying chart. Numerous repeat examinations were made on fluids and repeated punctures and on the whole the repeated test did not vary appreciably.

The reagent consists of a ten per cent tincture of gum benzoin in absolute ethyl alcohol, extracted with frequent shaking for one week and then filtered. Two-tenths of a cubic centimeter of this tincture is added drop by drop to fifteen cubic centimeters of distilled water in a 50 c.c. flask, agitating frequently and mixing well with the pipette; the flask is then placed in a hot water bath to bring it up to blood temperature. Thirteen three-inch Wassermann test tubes are now set up in a rack and into the first is pipetted 0.25 c.c. of distilled water, into the next 0.5 c.c., the next 1.5 c.c. and into each of the remaining tubes 1.0 c.c. from left to right. Of the spinal fluid 0.75 c.c. is now added to the first tube, 0.5 c.c. to the second and 0.5 c.c. to the third; after mixing 1.0 c.c. is removed from the third and mixed with the distilled water in the fourth tube; 1.0 c.c. from the fourth tube is taken, after mixing well, and placed in the fifth tube and so on. This dilution is continued to the twelfth tube from which the extra 1.0 c.c. is thrown out

and the thirteenth tube acts as a control on the reagent dilution. Higher dilutions may be made if necessary, but as the usual rack holds twelve tubes, and the reaction seldom goes further, twelve tubes have been found sufficient in this investigation. To each of these tubes is now added 1.0 c.c. of the reagent dilution and the tubes well agitated and set aside at room temperature. The flocculation usually commences in about one hour and may continue for about six hours; further flocculation rarely occurs after this time. It is preferable to make final readings after standing overnight. Readings are recorded for each tube as to the extent of flocculation that has taken place, by the following symbols. First, complete sedimentation with a clear supernatant fluid which will be designated as "three plus." Second, partial sedimentation showing a slight milkiness in the supernatant fluid will be designated as "two plus." Third, when a few flakes or flocculent masses are seen and the supernatant fluid is nearly as milky as the control tube, this will be designated as "one plus." When no reaction takes place the tubes remain as milky as the control tube; this is recorded as zero. Thus thirteen symbols, including the control tube, and each tube reading from left to right will show zones where the reaction has taken place. Negative and control tubes will remain in their original opaque condition for seventy-two hours with no evidence of sedimentation or flocculation.

As the investigation proceeded it became evident that the zone reactions placed various cases in a class by themselves: a classification of the cases by this zone grouping was attempted and it was found that if they were listed as tabetic, taboparetic, pareto-tabetic and paretic that the zone moved from right to left and also agreed with the clinical diagnosis. From these observations the number of tubes affected in a zone

CLASS	CASE Nº	TUBE NUMBER 1	2	3	4	5	6	7	8	9	10	11	12	13	GLOBULIN	WASSERMANN C.S.F.	WASSERMANN BLOOD	DIAGNOSIS
TABETIC	1	0	0	0	0	0	0	0	+++	+++	++	0	0	0	Positive	4 Plus	Neg.	TABES
	2	0	0	0	0	0	0	0	0	+++	+++	0	0	0	Positive	4 Plus	1 Plus	TABES
	3	0	0	0	0	0	0	0	+++	+++	0	0	0	0	Positive	4 Plus	Neg.	TABES
TABO-PARETIC	4	0	0	+++	+	0	0	0	+++	+++	++	++	0	0	Positive	4 Plus	4 Plus	TABES
PARETO-TABETIC	5	0	0	+++	+++	0	0	++	+++	+++	0	0	0	0	Positive	4 Plus	4 Plus	PARESIS
	6	++	+++	+++	+++	++	+++	+++	+++	+++	+++	0	0	0	Positive	4 Plus	4 Plus	PARESIS
	7	0	+	+	+	0	0	+++	+++	+++	+++	+	0	0	Positive	4 Plus	4 Plus	PARESIS
	8	0	0	+++	+++	0	0	+++	+++	+++	0	0	0	0	Positive	4 Plus	4 Plus	PARESIS
PARETIC	9	0	++	+++	0	0	0	0	0	0	0	0	0	0	Positive	4 Plus	Neg.	PARESIS
	10	0	++	+++	+++	+	0	+	+++	0	0	0	0	0	Positive	4 Plus	4 Plus	PARESIS
	11	0	0	+++	0	0	0	+	+	+	0	0	0	0	Positive	4 Plus	4 Plus	PARESIS
	12	+	+++	+++	+++	0	0	+	+++	+	0	0	0	0	Positive	4 Plus	Neg.	PARESIS
	13	0	++	+++	+++	0	0	0	+++	+	0	0	0	0	Positive	4 Plus	4 Plus	PARESIS
NO NEURO-SYPHILIS	14	0	0	0	0	0	0	0	0	0	0	0	0	0	Negative	Neg.	Neg.	INVOL. PSYCHOSIS
	15	0	0	0	0	0	0	0	0	0	0	0	0	0	Negative	Neg.	Neg	TREATED LUES
	16	0	0	0	0	0	0	0	0	0	0	0	0	0	Negative	Neg.	Neg.	PSYCHO-NEUROSIS
	17	0	0	0	0	0	0	0	0	0	0	0	0	0	Negative	Neg	Neg.	EPILEPTIC
	18	0	0	0	0	0	0	0	0	0	0	0	0	0	Negative	Neg	Neg.	TOXIC IRITIS
EXPERIMENTAL																		
	2	0	0	0	0	+++	+++	+++	+++	+++	+++	+++	+++	0	Bloody spinal fluid			
	2	0	0	0	0	0	0	0	+++	+++	+++	+++	+++	0	Bloody fluid cleared by centrifugation			
Negative Wass'n		0	0	0	+	++	+++	+++	+++	0	0	0	0	0	Average reading of blood serum			
Positive Wass'n		0	0	++	+++	+++	+++	+++	+++	+	0	0	0	0	Average reading of blood serum			
	6	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	++	0	0	Repeat on fluid 24 hours old			
	1	0	0	0	0	0	0	0	+++	+++	++	0	0	0	Repeat puncture 3 days later			

N.B. "0" denotes No Flocculation — "+" Slight — "++" Moderate — "+++" Complete

appears also to have a bearing on the severity of the patient's condition and the prognosis.

It appears that when the interstitial structures, meninges and spinal cord, are involved in the syphilitic progress, that the right zone, in the vicinity of the eighth dilution, is affected to varying degrees; if the involvement is purely parenchymatous then the left zone in the vicinity of the third dilution is the one in which the flocculation occurs. We see cases in which there seems to be involvement of both these portions of the nervous system, as evidenced in the test when a distinct tabetic zone reaction may be accompanied by a slight reaction in one or more tubes of the paretic zone or vice-versa, and the patient thought to be tabetic may show this evidence of incipient paresis which we were not expecting. This may be of great assistance in our prognosis of the case and the method of treatment. These factors seem very evident in this study and it is hoped they may be corroborated as the use of this test is continued.

Occasionally one tube will flocculate very early and in these cases it is well to repeat the test although usually the repeated test will show the same phenomenon, but some extraneous substance in the tube may be the cause and a repeated test will obviate any error from this cause. Also in a definite case of neuro-syphilis giving a negative finding the test should be done over. This occurrence was met with on only one occasion in this work and was in a case in which spinal fluid and blood Wassermann were both negative before treatment was begun, the globulin and cell count being positive, but a diagnosis of tabes was made and after institution of treatment the spinal fluid Wassermann became positive.

Every laboratory test has its peculiarities and the colloidal benzoin test is no exception.

The tests shown in chart form are from a variety of cases chosen from this investigation and are demonstrative of the zones affected by the spinal fluid of the various clinical types and a short review of some of them will not be amiss.

Case 3 was clinically a typical tabetic but a positive globulin test was the only laboratory finding. After Swift-Ellis treatment was instituted the fluid gave a four plus Wassermann reaction.

Case 4 was a typical tabetic with rather an acute onset and the patient was in a very irritable condition. Repeated examinations after Swift-Ellis treatment revealed a lessening of the reaction in the paretic zone with coincident clinical improvement.

Case 6 was put under malarial treatment after the spinal fluid examination, but had to be taken off as his physical condition was not good. He has improved to some extent and is being treated with tryparsamide.

Case 7 is a pareto-tabetic who on two occasions has had severe seizures of an epileptiform nature. He has had considerable treatment and shows marked tabetic symptoms.

Cases 8 and *11* have each had considerable treatment with arsphenamine, mercury, bismuth and tryparsamide and are now undergoing malarial treatment.

Case 9 was under malarial treatment when the puncture was done and had a temperature of 105°F. He had had no antisyphilitic treatment.

Cases 10 and *13* are both paretics in rather good condition some time after malarial treatment.

Case 12 has had extensive treatment with tryparsamide, arsphenamine, etc., and has had a good remission but shows some irritability and is being given malarial treatment.

Case 15 has been under my observation for nine years and was treated for syphilis in the secondary stage. His blood Wassermann has been negative for eight years.

Case 18 has had an iritis for one year. It has been diagnosed at various times as tubercular, toxic, and syphilitic. The patient gives no history of syphilis and has had repeated negative blood findings and shows no response to antisyphilitic treatment.

Conclusion.—The colloidal benzoin test of the spinal fluid is not a very complicated laboratory procedure and can be done with very little trouble and equipment. The test gives quite constant readings as repeated tests have shown. It gives a distinct zone in tabes and paresis and apparently shows when the interstitial and parenchymatous types of syphilis invade each other's territory.

In a study of the chart the following points are noted: True tabetics may show no parenchymal involvement. True paretics may show no interstitial involvement. Tabetics may show slight parenchymal involvement, and paretics may show slight interstitial involvement. This

is usually very evident in the patient's physical condition. So far in this investigation the Wassermann test and globulin test on the spinal fluid have been positive in each case in which the colloidal benzoin reaction has been positive and vice-versa.

It is to be hoped this test will be given a fair trial by other workers because of its simplicity and apparent diagnostic value.

The major portion of this investigation was done with the co-operation of the staff of the Ontario Hospital, Hamilton, and I desire to tender my thanks for their criticisms and suggestions.

Induced Hyperthyroidism.—In order to determine if possible whether or not harm may result from the routine use of iodine in the prophylaxis of goitre as it has been carried out in the Cleveland district since 1917, a study has been made by O. P. Kimball, Cleveland, of those cases of hyperthyroidism in which some form of iodine has been administered. In 309 cases it appeared that the symptoms of hyperthyroidism had been precipitated or made worse by the use of iodine. In 210 cases the goitres were of long standing, the average period being eighteen years. In each of these cases, the gland was clinically or microscopically adenomatous. In this group of 309 cases, there were six cases in which the only source of iodine had been iodized salt. All of these patients were women past forty years of age, and each had a nodular goitre of long standing. Thirty-seven patients had taken iodine of their own volition; several had taken a solution of sodium iodid, but the great majority had used repeated external applications of tincture of iodine over the goitre. The most striking fact brought out by this study is that five-sixths of the patients having induced hyperthyroidism had been taking iodine as prescribed by their physicians. In twenty-one cases of goitres of long standing, compound solution of iodine (Lugol's solution) had been given for weeks, in doses of from five to ten drops, three times a day. In many cases, five drops of the solution of sodium iodid, three times a day, had been prescribed, and a considerable number of these patients had taken this medication for as long as three or four months. One boy, aged sixteen years, who had a congenital adenoma, had taken syrup of ferrous iodid, 1 dram (3.75 c.c.), three times daily, continuously for eighteen months. In 84 per cent of the cases of toxic goitre the physicians had prescribed large doses of iodine to be taken over a long period of time, and this treatment had been given in spite of the fact that the goitre was of long standing and in many cases, nodular in type. Kimball says that, in all cases of iodine treatment, the dosage should be considered in terms of milligrams. The maximum dosage for an adult, provided there are no contraindications, is 10 mg. daily for not longer than one month, during which time the patient should be under very close observation. Long standing goitres in adults should be treated surgically, if any symptoms of hyperthyroidism are present. In young adults and in adolescents, medical treatment should first be tried. There is apparently no danger in the routine prophylaxis of goitre as it is carried out through the schools; namely, the administration of 10 mg. of iodine weekly. Among forty cases of exophthalmic goitre in children, only one child had been given iodine. In this case the patient had received the prophylactic treatment of 10 mg. of iodine a week for one month, three months before the onset of the acute hyperthyroidism, and a review of the history shows that the onset of the hyperthyroidism in this case was a coincidence and not a result of the month of iodine treatment. In the medical treatment of goitre in adults, Kimball emphasizes the importance of care in the selection of cases; the use of small amounts of iodine for not longer than one month, and the necessity of close observation throughout this period.—*Jour. Am. Med. Ass.*, Nov. 28, 1925.